REGISTRATION REPORT

Part B

Section 10: Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: GLOB1310aH

Product name(s): Glosset Ace

Chemical active substance(s):

Aclonifen, 540 g/L

Flufenacet, 60g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: Globachem NV

Submission date: December 2021

MS Finalisation date: 25/08/2022

After commenting: 14/12/2022

Version history

When	What
December 2021	Initial submission by the applicant for approval of new product.
August 2022	First zRMS PL evaluation
December 2022	Corrections made by zRMS PL after commenting round

Table of Contents

10 Relevance of metabolites in groundwater

10.1 General information

Aclonifen

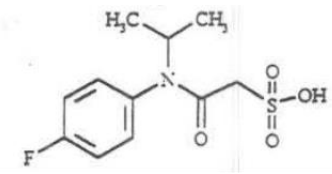
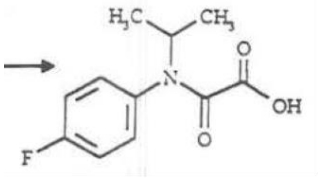
No metabolite was considered relevant for further exposure assessment in groundwater.

Flufenacet

The metabolites FOE-sulfonic acid (M2) and FOE oxalate (M1) are predicted to occur in groundwater at concentrations above 0.1 µg/L when the product Glosset Ace is applied on cereals (BBCH 00–09) at application rate of 90 g flufenacet/ha (see dRR Part B, Section 8, chapter 8.8). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.~~10~~ 11 (2021) is therefore ~~not~~ required.

General information on the metabolites is provided in Table 0-1. The impact of the relevance assessment on whether a particular GAP use leads to acceptable risk or not is presented in the summary of the cGAP evaluation in chapter 8.8 of the dRR Part B, Section 8 (Environmental fate and behaviour).

Table 0-1: General information on the metabolite(s)

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Flufenacet	FOE- sulfonic acid (M2)		Max PEC_{gw} Based on:	2.724940 µg/L FOCUS PEARL 4.4.4 tier 2 simulations for Jokioinen (2L/ha)
	FOE-oxalate (M1)		Max PEC_{gw} Based on:	0.140159 µg/L FOCUS PEARL 4.4.4 tier 2 simulations for Okehampton

10.2 Relevance assessment of FOE-sulfonic acid (M2)

Summary

The relevance of the groundwater metabolite FOE-sulfonic acid has already been assessed and the assessment agreed at EU level, and the relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 and 5 of the relevance assessment made at the EU-level are valid also with regard to the PEC_{gw} calculated for the GAP and groundwater scenarios considered in this dRR). FOE-sulfonic acid is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.~~10~~ 11. A summary of the relevance assessment is given in Table 0-1 and the corresponding studies are listed in the corresponding sections.

Table 0-1: Summary of the relevance assessment for FOE-sulfonic acid (M2)

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	2.724940 µg/L
			Based on	FOCUS PEARL 4.4.4 tier 2 simulations for Jokioinen (Use 3, 2L/ha pre-emergence)
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No
		Stage 2	Genotoxic properties of metabolite	Non-genotoxic
		Stage 3	Toxic properties of metabolite;	Less toxic than the parent
			Classification of parent	Acute Tox. ~~toxicity~~ ~~Cat~~ 4, H302 Skin Sens. ~~sensi~~. ~~Cat~~ 1, H317 STOT RE ~~Cat~~ 2, H373
			Classification of metabolite	Not required
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Refined risk assessment necessary (>0.75 µg/L)
	STEP 5		Refined risk assessment	acceptable
			Predicted exposure (% of ADI)	Max. 10.78% of ADI via drinking water – infant Max. 88% via diet
			ADI based on	Flufenacet ADI of 0.005 mg/kg bw (rat, 2 year study, safety factor: 250, Flufenacet, 7469/VI/98-Final, 3 July 2003)

~~* N/A: not applicable~~

10.2.1 STEP 1: Exclusion of degradation products of no concern

FOE-sulfonic acid does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

According to the guidance document on the assessment of the relevance of metabolites in groundwater (SANCO 221/2000-rev~~10~~ 11 ~~final~~, ~~2003~~ 2021), metabolites of no concern are:
• CO2 or an inorganic compound, not containing a heavy metal
• an organic compound of aliphatic structure (chain length < 4) which consist only of C, H, N, or O atoms
• a substance, which is naturally occurring and of no toxicological and ecotoxicological concern

None of the criteria are met for FOE-sulfonic acid (M2).

10.2.2 STEP 2: Quantification of potential groundwater contamination

Modelling studies:

PEC_{gw} calculations after leaching from soil for FOE-sulfonic acid were performed (see Part B, Section 8, chapter 8.8). The threshold of 0.1 µg/L is exceeded for FOE-sulfonic acid. Details are given in Part B, Section 8, chapter 8.8.

The FOCUS-PEARL, FOCUS-PELMO simulations were conducted over a period of 26 years and the 80th percentile of the annual average concentrations in leachate at 1 m depth for the last 20 years of each scenario was calculated. All predicted concentrations for flufenacet were <0.1µg/L. The maximum 80th percentile PEC_{GW} of the FOE sulphonic acid were 2.583456 µg/L, following the application of GLOB1310aH to winter cereals.

Lysimeter studies:

In the Draft Assessment Report for flufenacet (1997) two lysimeter studies, each with two lysimeters, were performed (DAR, 1997). In the first lysimeter study (corn-corn rotation) annual application rates of 480 g flufenacet/ha were used on corn at a pre-emergence stage. In the second lysimeter study (corn-winter wheat rotation) one application was performed at a rate of 480 g a.s./ha on corn at a pre-emergence stage. Later, in the same year a second application at a rate of 180 g a.s./ha was performed on wheat at a pre-emergence stage.

In the leachate, the active substance flufenacet and the metabolites M1 oxalate, M2 sulphonic acid, M3 alcohol and M4 thioglycolate sulfoxide were found. Only the metabolite M2 sulphonic acid was found at levels above 0.1 µg/L; all other metabolites were below this threshold value. An overview of the leachate concentrations of the potentially relevant metabolites M1 oxalate and M2 sulphonic acid is present-ed in the table below.

	Corn-corn rotation		Corn-winter wheat rotation	
	M2 sulfonic acid		M2 sulfonic acid	
	Lys. 15	Lys. 16	Lys. 17	Lys. 18
Maximum leachate at year 1 (µg/L)	1.295	1.094	3.4	3.7
Mean leachate at year 1 (µg/L)	0.573	0.474	1.42	1.69
Maximum leachate at year 2 (µg/L)	Not reported	Not reported	≤0.022*	
Mean leachate at year 2 (µg/L)	0.237	0.149	0.015*	

*single value for each lysimeter not reported

Due to the high application rates, the heavy rainfalls that occurred during the studies and the sandy soil used, it can be concluded that the lysimeter studies were performed reflecting very conservative condition for leaching.

Filed degradation studies:

In the DAR flufenacet (1997), soil dissipation studies were presented. In these studies, the metabolite M2 sulphonic acid and M1 oxalate were detected slightly above 0.01 mg/kg (limit of determination) in the 0-10 cm layer, the maximum value being 0.0208 mg/kg. In the study summary in the DAR (1997), it is not stated to which metabolite this value corresponds. No residues were detected in deeper layers.

While model calculations are performed making conservative assumptions in the scenario and parameter settings, lysimeter studies reflect in a more realistic level the fate of substances in the field and can therefore be regarded as higher tier in comparison to model calculations. As it was shown in the lysimeter

studies, only the metabolite M2 sulphonic acid was found in the leachate above the threshold value of 0.1 µg/L. The metabolite M1 oxalate was always found below this level, so the risk for groundwater contamination was not confirmed by the lysimeter studies. Thus, the RMS concluded that metabolite M1 oxalate does not pose a risk for groundwater if flufenacet is used according to the proposed use pat-tern.

The Scientific Committee on Plants (SCP) of the European Commission published an opinion concerning the evaluation of flufenacet in the context of council directive 91/414/EEC (SCP/FLUFEN/002-Final dated 17 October 2001). In this document the risk of M2 sulphonic acid to drinking water was assessed. According to SCP, the lysimeter studies may not represent a worst case scenario, since M2 sulphonic acid may show higher mobility at higher pH values, which were not considered in these studies. Thus, the lysimeter studies are only representative for sandy loam soils with a pH value < 7.0. Therefore, a maximum PEC_{GW} of 30 µg/L as estimated by PELMO modelling was used to assess its toxicity. The ADI (Acceptable Daily Intake) of flufenacet of 0.01 mg/kg body weight /day was taken as representative for M2 sulphonic acid. Assuming that the intake from drinking water does not exceed 10% of the ADI, the maximum acceptable daily intake via drinking water is therefore 1 µg/kg bw or 60 µg/day equal to the conservative estimate of daily exposure based on PELMO calculations (60 µg/day).

After evaluation of the lysimeter studies, the field degradation studies and modelling studies presented in the DAR (1997) and the risk to aquatic organisms and drinking water contamination, the Committee stated that no unacceptable risks for consumers are expected from exposure via drinking water to M2 sulphonic acid. Furthermore, the Committee indicated that the risk to non-target aquatic organisms is acceptable for the metabolite M2 sulphonic acid.

However the maximum 80th percentile PEC_{GW} of the metabolite FOE sulphonic acid was calculated to be 2.5834 µg/L are given in Part B, Section 8 in the core assessment. A further assessment is therefore needed.

10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.2.3.1 STEP 3, Stage 1: screening for biological activity

The available ecotoxicological data summarised during the EU review of flufenacet demonstrate that FOE-sulfonic acid does not have comparable or higher biological activity than the parent. However, new studies not previously considered within an EU peer review process are submitted in the frame of this application and are described in detailed in Appendix 2.

The metabolite is considered to be non-relevant and is further evaluated in Stage 2.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

The available genotoxicity studies summarized during the EU review of flufenacet show that there is no evidence for FOE-sulfonic acid being of genotoxic concern. The EC guidance states that the classification of the parent active substance should be used as pragmatic starting point for screening a metabolite. Since flufenacet is not classified as genotoxic, this suggests that the metabolites are of no toxicological concern.

Additionally, FOE-sulfonic acid was screened for genotoxic activity by the following data package of *in vitro* genotoxicity studies: Ames test, gene mutation test with mammalian cells, and a chromosome aberration test. FOE-sulfonic acid was non genotoxic as shown by a negative Ames test, negative gene mutation test and negative chromosome aberration test.

FOE-sulfonic acid is considered not relevant and is further evaluated in Stage 3.

The genotoxicity studies not reviewed on EU level are evaluated in Part B, Section 6 and its Appendix 2.

Study	Result	Reference
Bacterial reverse mutation Salmonella	Negative	Herbold BA, 2000 Report No. 29473 this study was submitted in first EU Flufenacet review and was evaluated in the DAR. Thus it is not subject to data protection
Mammalian cell gene mutation test using V79 cell line	Negative	Study No. 19-046
Mammalian chromosome aberration test	Negative	Report No. 2015-FRU-4

FOE-sulfonic acid (M02) resulted negative in the genotoxicity tests in bacteria and mammalian cells *in vitro* (bacterial reverse mutation, mammalian cell gene mutation) as well as in the *in vitro* chromosome aberration test.

10.2.3.3 STEP 3, Stage 3: screening for toxicity

The parent flufenacet to FOE sulfonic acid is not classified as acutely (category 1,2 or 3) or chronically toxic or very toxic, is not classified for reproductive toxicity and is not classified as a carcinogen in category 1 or 2 according to CLP 1272/2008).

Furthermore, the metabolite FOE-sulfonic acid is formed in rats. In the rat metabolism study performed with the parent compound flufenacet, FOE-sulfonic acid was detected in significant, but relatively low amounts of 0.5% of the dose in urine of male and female rats (Monograph of Flufenacet).

Based on the study results as well as on metabolic and structural considerations the metabolite FOE-sulfonic acid was considered to be of no toxicological relevance during the EU peer review. Thus, it was concluded that the metabolite FOE-sulfonic acid from a regulatory perspective can be qualified to be 'non-relevant' according to Step 3 of this assessment.

Overall, FOE-sulfonic acid is considered to be less toxic to humans than flufenacet. Further toxicity data for this metabolite are not considered to be necessary. As a worst case assumption, the ADI of the parent compound (0.005 mg/kg bw/day) is proposed to be used for the assessment of consumer exposure via ground- or drinking water to FOE-sulfonic acid.

FOE sulfonic acid is not considered relevant and is further evaluated in Step 4.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

Step 4 is required for metabolites not identified as relevant in the hazard assessment of Step 3, in order to make sure that any contamination of groundwater will not lead to unacceptable exposure of consumers via drinking water.

PECgw of FOE-sulfonic acid are above 0.75 µg/l and thus a further refined risk assessment is required. This is explained in 10.2.5.

10.2.5 STEP 5: Refined risk assessment

FOE sulfonic acid has a PEC_{gw} between 0.75 µg/L and 10 µg/L and thus the threshold of concern approach in Step 4 is not applicable. A refined assessment of the potential toxicological significance including the selected ADI is presented here.

Based on the hazard screening non-relevant metabolites require an exposure assessment to make sure that any contamination of groundwater will not lead to unacceptable exposure of consumers via their drinking water.

a) FOE-sulfonic acid

FOE-sulfonic acid is not a major metabolite in mammals, it is present at 0.5 – 1.0% of the total of administered parent compound. It is notable that FOE-sulfonic acid is expected to be more water soluble than the parent but has not been detected in urine or in kidney or liver. Hence there is no evidence of significant systemic exposure of FOE-sulfonic acid following gavage administration of flufenacet. FOE-sulfonic acid is the sulfonic acid metabolite of flufenacet and has therefore a similar structure. Furthermore, this sulfonic acid group makes the molecule more water soluble and it is unlikely that this metabolite is more toxic than the parent compound. This conclusion is supported by studies during the EU review of flufenacet. It is therefore considered appropriate to use the same ADI for FOE-sulfonic acid as for flufenacet (0.005 mg/kg bw).

a.1. Consumer exposure to FOE-sulfonic acid via drinking water

A consumer exposure assessment via drinking water is carried out based on an ADI of 0.005 mg/kg bw and using the maximum PECgw found in the Part B section 8, namely 2.72490 µg/L. However, because the groundwater concentrations are compared to a toxicological reference value expressed as flufenacet, also the concentration of the metabolite contained in drinking water must be expressed as parent equivalent. Thus, considering a molecular weight of ~~3636.3~~ 363.34 g/mol and 275.3 g/mol for flufenacet and FOE-sulfonic acid, respectively, the molecular conversion factor is 0.7578 and the corrected PECgw is 3.5958 µg/L.

For adults, assuming a 60 kg person drinks 2 litres of water per day, the drinking of water containing 3.5958 µg/L will result in a daily intake of 0.1199 µg sulfonic acid/kg bw x d. This represents 2.39% of the ADI.

In the case of toddlers assuming a 12 kg person drinks 1 litre of water per day, the drinking of water containing 3.5958 µg/L will result in a daily intake of 0.2996 µg FOE-sulfonic acid/kg bw x d. This represents 5.99% of the ADI.

For infants assuming a 5 kg person drinks 0,75 litre of water per day, the drinking of water containing 3.5958 µg/L will result in a daily intake 0.5393 µg FOE-sulfonic acid/kg bw x d. This represents 10.78 % of the ADI.

a.2. Consumer exposure to FOE-sulfonic acid via diet

For reason of simplification, the worst case assumption is made that plant residues consist to 100% of FOE sulfonic acid (thus no molecular weight conversion is applied). The portion of the TRR for the individual metabolites which is evident from the different metabolism studies is not considered in this approach.

The input values (MRLs) for the dietary risk assessment are reported in section 7, chapter 7.3.8.1. The calculation table according to EFSA PRIMo rev.2 3.1 is included in Appendix 3 of Section 7 and presented here below for clarity sake. The highest TMDI resulted in 88% of the ADI, which is considered the worst case situation. The risk is calculated considering all crops where a MRL is set, the MRL values are those from the parent according to Reg. (EC) No. 1127/2014. To keep a worst case approach, intake from animal products is included as some crops may be feed to animals, despite since no residues in food stuffs of animal origin are expected based on the EU review for flufenacet.
Predicted chronic consumer intakes of FOE-sulfonic acid is 88%.

European Food Safety Authority
EFSA PRIMo revision 3.1; 2019/03/19

FOE-sulfonic acid

LOQs (mg/kg) range from:	0.01	to:	0.05
Toxicological reference values			
ADI (mg/kg bw/day):	0.005	ARfD (mg/kg bw):	not necessary
Source of ADI:	EU review	Source of ARfD:	
Year of evaluation:	2012	Year of evaluation:	

Input values | Details - chronic risk assessment | Supplementary results - chronic risk assessment | Details - acute risk assessment/children | Details - acute risk assessment/adults

Comments:

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

TMDI/NEDI/IEDI calculation (based on average food consumption)	Calculated exposure (% of ADI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	Exposure resulting from: MRLs set at the LOQ (in % of ADI)	Exposure resulting from: commodities not under assessment (in % of ADI)
	88%	NL toddler	4.41	13%	Potatoes	12%	Milk: Cattle	11%	Apples	67%	
	57%	NL child	2.83	10%	Potatoes	8%	Sugar beet roots	8%	Wheat	38%	
	55%	DE child	2.73	12%	Apples	8%	Wheat	8%	Potatoes	38%	
	47%	GEMS/Food G06	2.33	14%	Wheat	6%	Potatoes	4%	Tomatoes	26%	
	45%	GEMS/Food G11	2.27	12%	Potatoes	7%	Wheat	4%	Soyabeans	25%	
	45%	GEMS/Food G08	2.24	12%	Potatoes	8%	Wheat	2%	Soyabeans	23%	
	44%	GEMS/Food G07	2.19	11%	Potatoes	8%	Wheat	2%	Soyabeans	23%	
	43%	GEMS/Food G15	2.16	11%	Potatoes	9%	Wheat	2%	Soyabeans	22%	
	43%	FR child 3 15 yr	2.13	9%	Wheat	5%	Milk: Cattle	5%	Potatoes	29%	
	42%	GEMS/Food G10	2.08	9%	Potatoes	8%	Wheat	3%	Soyabeans	24%	
	41%	RO general	2.05	11%	Potatoes	10%	Wheat	2%	Milk: Cattle	20%	
	40%	DK child	2.00	9%	Wheat	7%	Potatoes	6%	Rye	24%	
	39%	SE general	1.95	13%	Potatoes	6%	Wheat	4%	Bovine: Muscle/meat	20%	
	39%	UK toddler	1.95	10%	Potatoes	8%	Wheat	4%	Milk: Cattle	21%	
	39%	UK infant	1.94	10%	Potatoes	8%	Milk: Cattle	5%	Wheat	24%	
	37%	FR toddler 2 3 yr	1.87	6%	Wheat	6%	Milk: Cattle	6%	Potatoes	26%	
	36%	IE adult	1.78	7%	Potatoes	5%	Wheat	4%	Sweet potatoes	24%	
	35%	PT general	1.77	16%	Potatoes	8%	Wheat	2%	Wine grapes	12%	
	33%	ES child	1.67	9%	Wheat	6%	Potatoes	2%	Milk: Cattle	19%	
	29%	DE women 14-50 yr	1.45	5%	Sugar beet roots	4%	Wheat	3%	Potatoes	21%	
	29%	NL general	1.43	7%	Potatoes	4%	Wheat	3%	Sugar beet roots	17%	
	28%	DE general	1.42	4%	Sugar beet roots	4%	Wheat	4%	Potatoes	20%	
	27%	FI 3 yr	1.37	14%	Potatoes	2%	Wheat	1%	Bananas	11%	
	25%	IT toddler	1.24	13%	Wheat	3%	Potatoes	2%	Other cereals	9%	
	22%	FI 6 yr	1.10	12%	Potatoes	2%	Wheat	0.8%	Bananas	8%	
	21%	ES adult	1.04	5%	Wheat	3%	Potatoes	1%	Oranges	12%	
	20%	LT adult	1.02	10%	Potatoes	2%	Wheat	2%	Apples	9%	
	20%	FR infant	1.01	6%	Potatoes	3%	Milk: Cattle	2%	Apples	13%	
	19%	FR adult	0.97	4%	Wheat	2%	Wine grapes	2%	Potatoes	13%	
	17%	IT adult	0.87	8%	Wheat	2%	Potatoes	1%	Tomatoes	7%	
	17%	UK vegetarian	0.83	4%	Potatoes	4%	Wheat	0.9%	Oranges	8%	
	17%	PL general	0.83	10%	Potatoes	2%	Apples	0.9%	Tomatoes	6%	
	16%	DK adult	0.79	4%	Potatoes	2%	Wheat	1%	Milk: Cattle	10%	
	16%	UK adult	0.78	4%	Potatoes	3%	Wheat	1%	Wine grapes	8%	
	15%	FI adult	0.77	6%	Coffee beans	4%	Potatoes	0.7%	Rye	11%	
	7%	IE child	0.37	2%	Wheat	2%	Potatoes	0.7%	Milk: Cattle	3%	

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of FOE-sulfonic acid is unlikely to present a public health concern.

a.3. Consumer exposure to FOE-sulfonic acid via diet
In order to simplify the approach the calculation is performed based on conservative assumptions for intake of foods and water as follows:

Highest TDMI (%ADI)	**Highest exposure via drinking water (%ADI)**	**Highest combined exposure (%ADI)**
88% (NL toddler, potatoes)	10.78% (infant)	98.78%

Conclusions

From the dietary exposure calculations above it can be concluded that possible intakes of FOE sulfonic acid by means of drinking water and food of plant origin do not present a consumer health concern. The resulting highest combined exposure was 98.78%, but the calculations are based on several worst case assumptions, such as:

- For the reason of simplification it is assumed that for the chronic exposure calculation all residues of plant origin consist of FOE sulfonic acid.
- All commodities consumed contain residues of the flufenacet metabolite at the level of the MRL for flufenacet. However, actually the residue definition for enforcement covers all metabolites containing the

common fluorophenyl-isopropyl moiety. The distribution of individual metabolites according to the findings in the metabolism studies is not taken into account. Although no flufenacet derived residues can be expected in food of animal origin the MRL has been used in the TMDI calculation for animal commodities as well.
- No decrease of residues during storage and processing.
- Use of the upper limit groundwater concentrations for FOE sulfonic acid of 2.949 µg/L although the Joikionen scenario is not relevant in the Southern Zone and in many scenarios this concentration will be never reached.

zRMS: For metabolite FOE sulfonic acid (M2) sufficient information is available to conclude that the metabolite is non-relevant. The dietary exposure calculations indicates that possible intakes of FOE sulfonic acid by means of drinking water and food of plant origin do not present a consumer health concern. The calculations are based on several worst case assumptions and demonstrate an ADI (of flufenacet) usage of max. 98.78%. The consumer risk assessment shows an acceptable risk for FOE sulfonic acid. Thus the intended use of Glosset Ace does not pose a risk to consumers as a result of exposure to this metabolite.

10.3 Relevance assessment of FOE-oxalate (M1)

Summary

FOE oxalate is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 ~~rev.10~~ rev. 11 (2021). A summary of the relevance assessment is given in Table 10.3-1. Studies supporting PEC_{gw} data are evaluated in Section 8 (Environmental fate and behaviour). The data on biological activity are evaluated in Appendix 2 of this Section. The genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology). Input data for the refined risk assessment in Step 5 taking into account food as an additional source of possible intake by consumers are reported in Section 7 (Metabolism and residues). The dietary risk assessment for flufenacet is based on the "common moiety" residue definition for commodities of plant origin covering all metabolites which include the common N-fluorophenyl-acetamide moiety.

Table 10.3-1: Summary of the relevance assessment for FOE-oxalate (M1)

	Assessment step		**Result of assessment**	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.140159 µg/L
			Based on	FOCUS PEARL 4.4.4 tier 2 simulations for Okehampton (Use 3)
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	Lower biological activity than the parent

		Stage 2	Genotoxic properties of metabolite	Non-genotoxic
		Stage 3	Toxic properties of metabolite;	Less toxic than the parent
			Classification of parent	Acute Tox. ~~toxicity Cat~~ 4, H302 Skin Sens. ~~sensi. Cat~~ 1, H317 STOT RE ~~Cat~~ 2, H373
			Classification of metabolite	Not required
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Acceptable (<0.75 µg/L)
	STEP 5		Refined risk assessment	N/A*
			Predicted exposure (% of ADI)	N/A*
			ADI based on	N/A*

* N/A: not applicable

10.3.1 STEP 1: Exclusion of degradation products of no concern

FOE-oxalate does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

10.3.2 STEP 2: Quantification of potential groundwater contamination

Modelling studies:

PEC_{gw} calculations after leaching from soil for FOE-oxalate were performed (see Part B, Section 8, chapter 8.8). The threshold of 0.1 µg/L is exceeded for FOE-oxalate. Details are given in Part B, Section 8, chapter 8.8.

The FOCUS-PEARL, FOCUS-PELMO simulations were conducted over a period of 26 years and the 80th percentile of the annual average concentrations in leachate at 1 m depth for the last 20 years of each scenario was calculated. All predicted concentrations for flufenacet were <0.1µg/L. The maximum 80th percentile PECgw of the FOE oxalate was 0.140159 µg/L, following the application of GLOB1310aH to winter cereals.

Lysimeter studies:

In the Draft Assessment Report for flufenacet (1997) two lysimeter studies, each with two lysimeters, were performed (DAR, 1997). In the first lysimeter study (corn-corn rotation) annual application rates of 480 g flufenacet/ha were used on corn at a pre-emergence stage. In the second lysimeter study (corn-winter wheat rotation) one application was performed at a rate of 480 g a.s./ha on corn at a pre-emergence stage. Later, in the same year a second application at a rate of 180 g a.s./ha was performed on wheat at a pre-emergence stage.

In the leachate, the active substance flufenacet and the metabolites M1 oxalate, M2 sulphonic acid, M3 alcohol and M4 thioglycolate sulfoxide were found. Only the metabolite M2 sulphonic acid was found at levels above 0.1 µg/L; all other metabolites including M1 oxalate were below this threshold value. An overview of the leachate concentrations of the potentially relevant metabolite M1 oxalate is presented in the table below.

	Corn-corn rotation		Corn-winter wheat rotation	
	M1 oxalate		M1 oxalate	
	Lys. 15	Lys. 16	Lys. 17	Lys. 18
Maximum leachate at year 1 (µg/L)	0.007	0.006	≤0.04*	
Mean leachate at year 1 (µg/L)	0.001	0.001	0.012*	
Maximum leachate at year 2 (µg/L)	0.041*		≤0.022*	
Mean leachate at year 2 (µg/L)	<0.018	<0.014	0.009*	

*single value for each lysimeter not reported

Due to the high application rates, the heavy rainfalls that occurred during the studies and the sandy soil used, it can be concluded that the lysimeter studies were performed reflecting very conservative condition for leaching.

Filed degradation studies:

In the DAR for flufenacet (1997), soil dissipation studies were presented. In these studies, the metabolite M2 sulphonic acid and M1 oxalate were detected slightly above 0.01 mg/kg (limit of determination) in the 0-10 cm layer, the maximum value being 0.0208 mg/kg. In the study summary in the DAR (1997), it is not stated to which metabolite this value corresponds. No residues were detected in deeper layers.

While model calculations are performed making conservative assumptions in the scenario and parameter settings, lysimeter studies reflect in a more realistic level the fate of substances in the field and can therefore be regarded as higher tier in comparison to model calculations. As it was shown in the lysimeter studies, only the metabolite M2 sulphonic acid was found in the leachate above the threshold value of 0.1 µg/L. The metabolite M1 oxalate was not detected above 0.1µg/L

However the maximum 80th percentile PECgw of the metabolite FOE oxalate was calculated to be 0.140159 µg/L are given in Part B, Section 8 in the core assessment. A further assessment is therefore needed.

10.3.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.3.3.1 STEP 3, Stage 1: screening for biological activity

The available ecotoxicological data summarised during the EU review of flufenacet demonstrate that FOE-sulfonic acid does not have comparable or higher biological activity than the parent. However, new studies not previously considered within an EU peer review process are submitted in the frame of this application and are described in detailed in Appendix 2.

The metabolite is considered to be non-relevant and is further evaluated in Stage 2.

10.3.3.2 STEP 3, Stage 2: screening for genotoxicity

The available genotoxicity studies summarized during the EU review of flufenacet show that there is no evidence for FOE-oxalate being of genotoxic concern.

FOE-oxalate was screened for genotoxic activity by means of Ames test, gene mutation test with mammalian cells and a chromosome aberration test. FOE oxalate was non genotoxic as shown by a negative Ames test, negative gene mutation with mammalian cells and negative chromosome aberration test.

FOE-oxalate is considered not relevant and is further evaluated in Stage 3.

The genotoxicity studies not reviewed on EU level are evaluated in Part B, Section 6 and its Appendix 2.

Study	Result	Reference
Bacterial reverse mutation Salmonella	Negative	Siveneau C, 2016; 2015-FRU-1
Mammalian cell gene mutation test using	Negative	Siveneau C, 2016; 2015-FRU-5
Mammalian chromosome aberration test	Negative	Peroche, A, 2016; 2015-FRU-3

FOE-oxalate (M01) resulted negative in the genotoxicity tests in bacteria and mammalian cells *in vitro* (bacterial reverse mutation, mammalian cell gene mutation) as well as in the *in vitro* chromosome aberration test.

10.3.3.3 STEP 3, Stage 3: screening for toxicity

The parent flufenacet to FOE oxalate is not classified as acutely or chronically toxic or very toxic, is not classified for reproductive toxicity and is not classified as a carcinogen in category 1 or 2 according to CLP 1272/2008). There are no reasons to expect that FOE-oxalate may be toxic or highly toxic.

FOE-oxalate is not a rat metabolite, but is detected in plants and groundwater. The bioavailability of FOE-oxalate was investigated in rats after one single oral application of 1 mg/kg bw (Monoggraph Flufenacet). The metabolite was rapidly excreted with faeces (61-80% of the dose) and with urine (19-37%) of the dose within 24hours after dosing. FOE-oxalate was identified as unchanged in both faeces and urine, demonstrating that if FOE-oxalate is absorbed it is not metabolized and not accumulated in the body, but rapidly excreted instead. On the basis of the toxicological and animal metabolism studies it can be concluded that the bioavailability for FOE-oxalate is low compared to the parent flufenacet. The results of the livestock metabolism studies are in line with the mentioned information, FOE-oxalate was not metabolized and it was found up to 99% TRR in goat kidney. Moreover, the low levels in tissue, milk and eggs suggest that FOE-oxalate is minimally absorbed and quickly excreted after oral administration (Monograph Flufenacet).

Furthermore, the metabolite FOE-sulfonic acid is formed in rats. In the rat metabolism study performed with the parent compound flufenacet, FOE-sulfonic acid was detected in significant, but relatively low amounts of 0.5% of the dose in urine of male and female rats (Monograph of Flufenacet).

Furthermore, the structure necessary for the biological activity of flufenacet is not maintained in FOE-oxalate. In addition, FOE-oxalate is a secondary metabolite after FOE-alcohol which gives little concern . It was concluded during the EU review that FOE-oxalate should give rise to little concern

Even if exposure due to intake of water occurs, FOE-oxalate will not be metabolized, but instead it will be rapidly excreted unchanged. Therefore, it can be considered that FOE-oxalate will be less toxic to humans that the parent flufenacet.

FOE-oxalate is not considered relevant and is further evaluated in Step 4.

10.3.4 STEP 4: Exposure assessment – threshold of concern approach

Step 4 is required for metabolites not identified as relevant in the hazard assessment of Step 3. FOE-oxalate was not considered relevant in the hazard assessment of Step 3.

The maximum PECgw of FOE-oxalate was 0.140159 µg/L. The concentration of FOE oxalate, which is considered toxicologically not relevant, in drinking water is below a threshold of 0.75 µg/L set in EC

guidance document SANCO/221/2000 –rev.~~10~~ 11 (2021), therefore it is considered that it poses low risk to consumers and a refined risk assessments for this non-relevant metabolite is not necessary, however, the potential exposure to FOE oxalate via plant-derived products cannot be excluded, as FOE oxalate is a main plant metabolite.

10.3.5 STEP 5: Refined risk assessment

Not required for FOE-oxalate since the threshold of 0.75 µg/L is not exceeded.
According to the guidance document SANCO/221/2000–rev. 11 (2021) further assessment is not required, but given that it is a major metabolite the calculation of consumer exposure (with water and diet) is presented below.
Based on the findings from plant metabolism studies, the residue definition in plants was defined as flufenacet (sum of all compounds containing the N fluorophenyl-N-isopropyl moiety expressed as flufenacet equivalent). It covers all the metabolites derived from the fluorophenyl-acetamide moiety, i.e. including FOE oxalate (M01).
The ADI of the parent compound (0.005 mg/kg) is considered as an adequate reference value for the assessment of consumer exposure to FOE oxalate. EFSA concluded in their Reasoned Opinion on the review of existing MRLs (EFSA Journal 2012;10(4):2689): "However, since none of the metabolites [containing the N fluor-ophenyl-N-isopropyl moiety] raised any particular concern it is considered acceptable to apply the toxicological reference values of the parent compound for the time being."

Consumer exposure to FOE oxalate

A consumer exposure assessment via drinking water is carried out based on an ADI of 0.005 mg/kg bw and using the maximum PECgw found in the Part B section 8, namely 0.140159 µg/L. However, because the groundwater concentrations are compared to a toxicological reference value expressed as flufenacet, also the concentration of the metabolite contained in drinking water must be expressed as parent equivalent. Thus, considering a molecular weight of 363.34 g/mol and 225.2 g/mol for flufenacet and FOE-oxalate, respectively, the molecular conversion factor is 1.22 and the corrected PECgw is 2.23 µg/L.

For adults, assuming a 60 kg person drinks 2 litres of water per day, the drinking of water containing 2.23 µg/L will result in a daily intake of 0.00446 µg oxalate/kg bw x d. This represents 1.49% of the ADI.

In the case of toddlers assuming a 12 kg person drinks 1 litre of water per day, the drinking of water containing 2.23 µg/L will result in a daily intake of 0.00223 µg FOE oxalate/kg bw x d. This represents 3.72% of the ADI.

For infants assuming a 5 kg person drinks 0,75 litre of water per day, the drinking of water containing 2.23 µg/L will result in a daily intake 0.00167 µg FOE oxalate/kg bw x d. This represents 6.68 % of the ADI.

Consumer exposure to FOE oxalate via diet

The input values (MRLs) for the dietary risk assessment are reported in section 7, chapter 7.3.8.1. The highest TMDI resulted in 88% of the ADI, which is considered the worst case situation. The risk is calculated considering all crops where a MRL is set, the MRL values are those from the parent according to Reg. (EC) No. 1127/2014. Predicted chronic consumer intakes of FOE oxalate is 88%.
In order to simplify the approach the calculation is performed based on conservative assumptions for intake of foods and water as follows:

Highest TDMI (%ADI)	**Highest exposure via drinking water (%ADI)**	**Highest combined exposure (%ADI)**

88% (NL toddler, potatoes)	6.68% (infants)	94.68%

Conclusions

From the dietary exposure calculations above it can be concluded that possible intakes of FOE oxalate by means of drinking water and food of plant origin do not present a consumer health concern. The resulting highest combined exposure was 94.68%, but the calculations are based on several worst case assumptions.

zRMS: For metabolite FOE oxalate (M1) sufficient information is available to conclude that the metabolite is non-relevant. The dietary exposure calculations indicates that possible intakes of FOE sulfonic acid by means of drinking water and food of plant origin do not present a consumer health concern. The calculations are based on several worst case assumptions and demonstrate an ADI (of flufenacet) usage of max. 98.78%. The consumer risk assessment shows an acceptable risk for FOE sulfonic acid. Thus the intended use of Glosset Ace does not pose a risk to consumers as a result of exposure to this metabolite.

Appendix 1 Lists of data considered in support of the evaluation

Tables considered not relevant can be deleted as appropriate.

MS to blacken authors of vertebrate studies in the version made available to third parties/public.

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCA Section 3	Tabary, F.	2015	Screening of Biological Efficacy of Flufenacet metabolites compared to parent Flufenacet, FRANCE, 2015. Staphyt, Study No.: FTY-16-23370-FR01, GLP/GEP: no Not published	N	Task Force Flufenacet

List of data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
-	-	-	-	-	-

The following tables are to be completed by MS

List of data submitted by the applicant and not relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	Y/N	Owner

List of data relied on not submitted by the applicant but necessary for evaluation

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	Y/N	Owner

Appendix 2 Additional information

Comments of zRMS:	The aim of the study was to evaluate the biological activity of two flufenacet metabolites: FOE-sulfonic acid (M02) and FOE-oxalate (M01) and comparison of the activity to the parent substance. The parent flufenaced was effective in weed control, while the two metabolites did not have such an effect. Thus it can be concluded that none of the metabolites tested has a significant biological activity, compared to the active substance. The study presented below is regarded as supplementary information.

Reference:	KCA Section 3
Report	Tabary F. 2015. Screening of Biological Efficacy of Flufenacet metabolites compared to parent Flufenacet, FRANCE, 2015. Staphyt, Study No.: FTY-16-23370-FR01,
Guideline(s):	Not specified
Deviations:	No
GLP:	No
Acceptability:	Yes

Materials and methods

This trial was set up in order to evaluate the biological activity of different metabolites (M1, M2, M7, M9, TFA, TFESA) compared to the parent flufenacet on annual grasses and annual dicotyledonous weeds. These weeds were specifically selected as it is known that they are either resistant or sensitive to the parent active substance. The trial was located in France and conducted under controlled greenhouse conditions.

The application rates applied was 240 g a.s./ha targeted for the parent flufenacet and corrected for molecular weight for the metabolites. All products were diluted with commercial acetone before being diluted in water.

Test material	**Molar mass**	**Rate**
FOE-sulfonic acid (M02)	275.3 g/mol	0.1819 kg/ha
FOE-oxalate (M01)	225.2 g/mol	0.1488 kg/ha
Flufenacet	225.2 g/mol	0.240 kg/ha
Control	-	-

The plant species tested were the following:

Code	**Name**	**Common name**
APESV	*Apera spica-venti*	Silky bent grass
ALOMY	*Alopecurus myosuroides*	Black grass
POAAN	*Poa annua*	Annual meadow grass
STEME	*Stellaria media*	Common chickweed
MATCH	*Matricaria recutia*	Scented may weed

Results and discussions

Evaluation interval	**14 DA-A**				
Pest Code	**APESV**	**ALOMY**	**POAAN**	**STEME**	**MATCH**
Pest stage Majority	**11-12**	**11-12**	**11-12**	**12-14**	**13-14**
Rating type	**Control**				
Rating unit	**%**				

Treatment	**Rate (kg/ha)**					
M01	0.1488	0.0	0.0	0.0	0.0	0.0
M02	0.14819	0.0	0.0	0.0	0.0	0.0
Flufenacet	0.240	50.0	15.0	0.0	0.0	0.0
Control	-		-	-	-	-

Two weeks after application, the parent flufenacet demonstrated a significant effect of thinning and volume reduction on *Apera spica-venti* and *Alopecurus myosuroides* compared to the untreated control. No effect was visible on *Poa annua*, *Stellaria media* and *Matricaria recutita*. None of the metabolites showed any effect on the tested species.

Evaluation interval		**28 DA-A**				
Pest Code		**APESV**	**ALOMY**	**POAAN**	**STEME**	**MATCH**
Pest stage Majority		**21**	**21**	**21-23**	**19**	**19**
Rating type		**Control**				
Rating unit		**%**				
Treatment	**Rate (kg/ha)**					
M01	0.1488	0.0	0.0	0.0	0.0	0.0
M02	0.14819	0.0	0.0	0.0	0.0	0.0
Flufenacet	0.240	70.0	61.7	61.7	0.0	0.0
Control	-		-	-	-	-

Four weeks after application, the biological efficacy of the parent flufenacet was confirmed on grasses with 60-70% of efficacy (thinning and volume reduction) compared to the untreated controls. Metabolites M1 and M2 did not show any effect.

Conclusion

Based on the above results, it can be concluded that none of the metabolites tested has a significant biological activity, compared to the active substance.